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Swiss Science Concentrates

A CHIMIA Column

Short Abstracts of Interesting Recent Publications of Swiss Origin

Exploring Simple Drug Scaffolds from the Generated Database Chemical Space Reveals a Chiral Bicyclic Azepane with Potent Neuropharmacology

Aline Carrel, Adonis Yiannakas, Jaap-Jan Roukens, Ines Reynoso-Moreno, Markus Orsi, Amol Thakkar, Josep Arus-Pous, Daniele Pellegata, Jürg Gertsch, and Jean-Louis Reymond*

J. Med. Chem. **2025**, *68*, 9176
https://doi.org/10.1021/acs.jmedchem.4c02549
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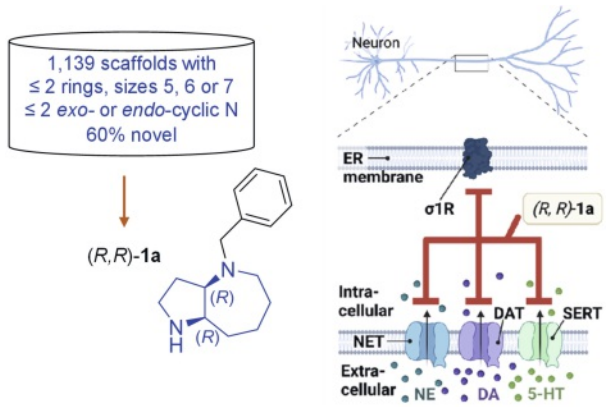
This study investigates the untapped potential of simple, synthetically accessible amine scaffolds derived from the ring system database (GDB-4c). The researchers enumerated 1,139 mono- and bicyclic amine scaffolds composed of five-, six-, or seven-membered rings, identifying 680 previously unreported structures. Several novel *cis*- and *trans*-fused azepanes were synthesized, with the *N*-benzylated compound (*R*,*R*)-1a emerging as a potent nanomolar inhibitor of norepinephrine (NET, SLC6A2, IC_{50} = 60 ± 7 nM) and dopamine transporters (DAT, SLC6A3, IC_{50} = IC50 = 230 ± 12 nM), as well as σ-1R (IC_{50} ≈ 110 nM). This compound demonstrated excellent brain penetration, stereoselective activity, and robust effects in behavioral and metabolomic assays in mice, including strong yet reversible sedation and changes in neurotransmitter levels. These results highlight the power of systematic enumeration and synthesis-guided screening of simple ring systems as a strategy to uncover structurally novel and pharmacologically rich chemical matter, offering a broadly applicable framework for early-stage drug discovery.

Authors' comments:
"This project started with a very simple idea which later became a rich source of inspiration, synthetic challenges, and surprises. It highlights that intrinsically simple scaffolds are often underexplored, yet hold great potential for drug discovery.



NMR²-Based Drug Discovery Pipeline Presented on the OncogenicProtein KRAS

Matthias Bütikofer, Felix Torres, Harindranath Kadavath, Nina Gämperli, Marie Jose Abi Saad, Daniel Zindel, Nicolas Coudevylle, Roland Riek*, and Julien Orts*

J. Am. Chem. Soc. **2025**, *147*, 13200
https://doi.org/10.1021/jacs.4c16762
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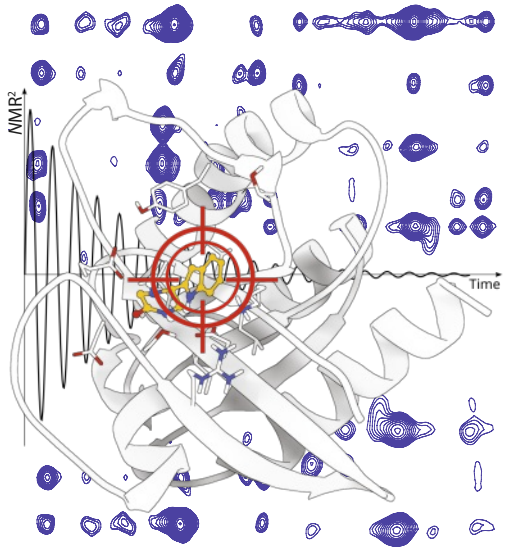
This study presents the first comprehensive use of NMR molecular replacement (NMR^2) in a fragment-based drug discovery pipeline targeting KRAS G12V. A library of 890 fragments were screened by NMR, identifying hits binding the key switch SI/II region. Binding modes were elucidated using NMR^2, without requiring full resonance assignment. A novel relaxation-based filtered NOESY sequence enabled accurate structure determination without isotope ^{13}C and ^{15}N labeling, validated against traditional labeled protocols. Twelve KRAS–fragment complex structures were resolved, guiding structure–activity relationship analysis and ligand optimization. This streamlined approach expands NMR's applicability, especially when X-ray crystallography is not viable, and supports efficient hit validation and lead development.

Authors' comments:
"This powerful method enables rapid in-house structure elucidation. Our vision is to make NMR the most versatile and indispensable tool for structure-based drug design, fully integrated into medicinal chemistry."



Prepared by James Southwell, Cesare Berton, Jonas Genz, Stanislav Prytuliak, Fan Liu, Eda Nisli, Deborah Bäcker, Samy Kichou, Dominik Ernst, Tiago Rosa de Araujo, Liam Wenger, Ian Saxer, Zuzana Simackova, Henrik Braband, and Jason P. Holland*
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Please contact jason.holland@chem.uzh.ch

Metal-Assisted Synthesis of Extended Polyaromatic Nitrogen-Rich Ligands for Tunable Sensitization of Eu(III) Complexes

Giau Le-Hoang, Laure Guénée, Melanda Bertrand-Avebe, Lucille Babel, Arnulf Rosspeintner, and Claude Piguet*
Inorg. Chem. **2025**, *64,* 3941
https://doi.org/10.1021/acs.inorgchem.4c05202
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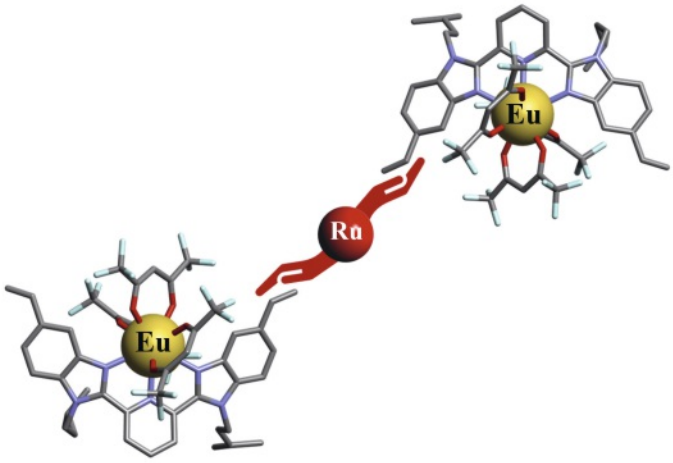
This study introduces a metal-assisted acyclic diene metathesis (ADMET) polymerization strategy to synthesize nitrogen-rich oligomeric and polymeric ligands from monomers where europium complexation is crucial for catalyst protection and polymer formation. Extended π-conjugation in the resulting structures lead to red-shifted excited states with lower photoluminescence quantum yields due to back energy transfer. These europium(III) complexes have broad applications in solar cells, LEDs, and biomedical probes. By overcoming limitations in luminescent lanthanide assemblies, this work enables the design of alternating multiple tridentate–didentate or tridentateA–tridentateB strands for the design of controlled heterometallic d–f or f–f′ metallopolymers, thus advancing tailored luminescent materials for cutting-edge technologies.

Authors' comments:
"Earth-abundant europium metals are used to allow rarest ruthenium catalysts to connect monomeric nitrogen-rich ligands."



Squaraine Dyes for Organic Photomultiplication Photodetectors with 220% External Quantum Efficiency at 1240 nm

Joshua Csucker, Elodie Didier, João P. F. Assunção, Daniel Rentsch, Radha Kothandaraman, Dominik Bachmann, Ivan Shorubalko, Frank Nüesch, Roland Hany*, and Michael Bauer

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https://doi.org/10.1002/advs.202502320
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Near-infrared (NIR) photodetectors (PDs) find broad applications ranging from industrial product monitoring to machine automation systems. Typically, inorganic sensor materials such as indium, gallium, and arsenide are utilised for detecting light beyond 1100 nm. Recently the demand for lightweight and mechanically compliant NIR PDs has led to the emergence of organic semiconductors as promising alternative materials, due to their tunable optical and chemical properties. However, the library of organic dyes with peak absorption beyond the cut-off of silicon is very small. In this work, the combination of strong electron-accepting and -donating groups is utilised to design and synthesise novel squaraine dyes with superior absorption characteristics, displaying maximum absorption above 1100 nm in solution and 1200 nm in the film. Squaraine dye-based NIR PDs exhibit an external quantum efficiency (EQE) of 220% at 1240 nm (1 eV) and still maintain an EQE of 25% in the absorption tail at 1400 nm, thereby surpassing existing NIR organic PD designs.

Authors' comments:
"A wide range of applications use invisible near-infrared light for sensing and imaging. Easy-to-make organic-based devices able to see light beyond 1100 nm allow for completely new avenues in wearable health monitoring or semiconductor technologies."